Health Canada Santé Canada

Guidance Document

Applications for Medical Device Investigational Testing Authorizations

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Canada

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Foreword

Guidance documents are meant to provide assistance to industry and health care professionals on how to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent, and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant programme area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, effectiveness, or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable Guidance documents.

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1. Introduction

The Food and Drugs Act (FDA) sets out the legislative framework under which medical devices are regulated. The Medical Devices Bureau is responsible for administering the requirements within Part 3 of the Medical Devices Regulations (herein referred to as the Regulations) that govern the sale and importation of a medical device for investigational testing involving human subjects. Manufacturers and importers must meet the regulatory requirements therein including requirements outlined in subsection 83(1) of the Regulations in order to receive authorization from Health Canada to sell a device to a qualified investigator for the purpose of conducting investigational testing.

1.1 Policy objectives

To provide assistance to manufacturers and importers in preparing the documentation necessary to obtain an authorization for the sale or importation of a medical device under an Investigational Testing Authorization (ITA), while assuring the protection of research subjects, and promoting excellence in research and development in Canada. In doing so, Health Canada endeavors to improve access to new and innovative medical device technologies for Canadians.

1.2 Policy statements

Manufacturers and importers are required to submit ITA applications to Health Canada in order to sell or import a medical device for the purpose of conducting investigational testing in human subjects.

Health Canada's expectation is that manufacturers follow the principles of the Declaration of Helsinki and the Tri-Council Policy Statement (2nd Edition): Ethical Conduct for Research Involving Humans (2014), and conform to Good Clinical Practices (GCP) as set out by ISO 14155 - Clinical investigation of medical devices for human subjects. ISO 14155 is generally consistent with the definitions and requirements of the Regulations. Where inconsistencies exist, the Regulations take precedence.

Research Ethics Boards (REBs) play an important role in the oversight of the conduct of investigational testing, and REB information is required for all clinical trials involving medical devices by Part 3, section 81 of the Regulations. Health Canada will issue a "Letter of Authorization" for investigational testing of Class III and IV medical devices, if the application meets the requirements stated in Part 3 of the Regulations, although REB approval may not be available at the time the ITA application review has been completed. **Manufacturers and importers are reminded that this information is required prior to study initiation, and for Class III and IV medical devices, the REB approval letter must be submitted to Health Canada as soon as it becomes available.**

Manufacturers and importers are requested to submit ITA applications in the "non-eCTD electronic-only" format and follow the structure presented in Appendix 4.

1.3 Scope and application

This guidance document is intended to assist manufacturers and importers with organizing and submitting an ITA application to conduct investigational testing of a Class II, III or IV device, by the manufacturer, an academic institution, a health care facility or a contract research

organization. It also provides details on the responsibilities of manufacturers and importers when conducting investigational testing using Class I devices. Further, it will assist investigators and institutions involved in the investigational testing of medical devices in Canada to understand their roles and responsibilities in this process.

This document is not applicable to the investigational testing of in vitro diagnostic devices (IVDDs) in Canada. Manufacturers and importers are referred to the guidance document titled Preparation of an Application for Investigational Testing - in vitro Diagnostics (GD010) available on the Government of Canada website (refer to Appendix 2).

This guidance document supersedes the previous guidance document titled: Preparation of an Application for Investigational Testing - Medical Devices (GD009/Rev00-MDB V3 dated 1999-02-22).

1.4 Background

Investigational testing of medical devices in human subjects has become a growing area for research and development in Canada since the establishment of the new Medical Devices Regulations in May, 1998.

This guidance document has been updated from the previous guidance document published in 1999 to add clarity, respond to stakeholder concerns and address topics such as: the use of recognized standards under the Regulations, drug-device combination products, the use of unlicensed devices in drug studies, timing of REB approval for Class III and IV medical devices, investigator-sponsored investigational testing, stages of product development, revisions to an investigational testing protocol, and problem reporting. Moving forward, Health Canada intends to review this guidance document regularly to respond to stakeholder concerns and a rapidly changing medical device landscape within Canada.

2. Guidance for implementation

2.1 Abbreviations and definitions[1]

2.1.1 Abbreviations

CTA
Clinical Trial Application (drugs and biologics)

CTD
Common Technical Document

GCP
Good Clinical Practices

IA
Investigator Agreement

IB
Investigator's Brochure

ICF
Informed Consent Form

IFU
Instructions for Use

IT
Investigational Testing

ITA
Investigational Testing Authorization

IVDD
In-Vitro Diagnostic Devices

ISO
International Organization for Standardization

MDB
Medical Devices Bureau

MDCU
Medical Devices Compliance Unit

MDPR
Medical Devices Problem Reporting

RCT
Randomized Controlled Trial

REB
Research Ethics Board

TPD
Therapeutic Products Directorate

2.1.2 Terms and definitions

Most of the definitions listed below were taken from the Regulations and ISO 14155 Clinical investigation of medical devices for human subjects - Good Clinical Practice.

Additional Information:
Information requested from the device manufacturer or importer by Health Canada to determine whether the conditions set out in subsection 83(1) of the Regulations have been met.

Adverse Event:
Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device which includes:

a. events related to the investigational medical device or the comparator; and
b. events related to the procedures involved

For users or other persons, this definition is restricted to events related to investigational medical devices.

Bias:

A systematic error in measurement during data collection.

Case Report Forms:

Set of printed, optical or electronic documents for each subject on which information to be reported to the sponsor is recorded, as required by the Clinical Investigation Plan (i.e., protocol).

Clinical investigation:

A systematic investigation in one or more human subjects, undertaken to assess the safety and/or performance of a medical device[2].

Clinical Investigation Report:

Document describing the design, execution, statistical analysis and results of a clinical investigation.

Combination Product:

Is a therapeutic product that combines a drug or biologic component and a device component (which by themselves would be classified as a drug or a device), such that the distinctive natures of the drug or biologic component and device component are integrated into a single product.

Comparator:

Medical device, therapy (e.g., active control), placebo, sham, or no treatment, used in the reference group in a clinical investigation.

Contract Research Organization:

Person or organization contracted by the sponsor[3] to perform one or more of the sponsor's clinical investigation-related duties and functions.

Deviation:

Instance(s) of failure to follow, intentionally or unintentionally, the requirements of the Clinical Investigation Plan.

Device:

means an instrument, apparatus, contrivance or other similar article, or an in vitro reagent, including a component, part or accessory of any of them, that is manufactured, sold or represented for use in:

a. diagnosing, treating, mitigating or preventing a disease, disorder or abnormal physical state, or any of their symptoms, in human beings or animals
b. restoring, modifying or correcting the body structure of human beings or animals or the functioning of any part of the bodies of human beings or animals
c. diagnosing pregnancy in human beings or animals
d. caring for human beings or animals during pregnancy or at or after the birth of the offspring, including caring for the offspring, or
e. preventing conception in human beings or animals

however, it does not include such an instrument, apparatus, contrivance or article, or a component, part or accessory of any of them, that does any of the actions referred to in

paragraphs (a) to (e) solely by pharmacological, immunological or metabolic means or solely by chemical means in or on the body of a human being or animal.

Device Identifier:

Means a unique series of letters or numbers or any combination of these or a bar code that is assigned to a medical device by the manufacturer and that identifies it as different from similar devices.

Device Name:

In respect of a medical device, includes any information necessary for the user to identify the device and to distinguish it from similar devices.

Emergency:

"An unlooked for or sudden occasion; an accident; an urgent or pressing need"[4].

Ethics Committee:

Independent body whose responsibility it is to review clinical investigations in order to protect the rights, safety and well-being of human subjects participating in a clinical investigation. The regulatory requirements pertaining to ethics committees or similar institutions vary by country or region[5].

Good Clinical Practices:

Generally accepted clinical practices that are designed to ensure the protection of the rights, safety and well-being of clinical trial subjects and other persons.

Health Care Professional:

Means a person who is entitled under the laws of a province to provide health services in that province.

Hypothesis:

Testable statement, resulting from the objective, regarding the investigational medical device safety or performance that is used to design the clinical investigation and that can be accepted or rejected based on results of the clinical investigation and statistical calculations. The primary hypothesis is the determinant of the investigational medical device safety or performance parameters and is usually used to calculate the sample size. Secondary hypotheses concerning other points of interest can also be evaluated.

Importer:

A person other than the manufacturer of a device, whose establishment is in Canada, who causes the medical device to be brought into Canada from foreign manufacturers or distributors, for sale in Canada.

Independent:

Not involved in the conduct of a clinical investigation, except for their specifically assigned responsibilities, in order to avoid bias or a conflict of interest.

Informed Consent Document/Form:

Process by which an individual is provided information and is asked to voluntarily participate in a clinical investigation. Informed consent is documented by means of a written, signed and dated informed consent form.

Investigation Site:

Institution or site where the clinical investigation is carried out[6].

Investigational Medical Device:

Medical device being assessed for safety or performance in a clinical investigation. This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes[7].

Investigator:

Individual member of the investigation site team designated and supervised by the principal investigator at an investigation site to perform critical clinical-investigation-related procedures or to make important clinical investigation-related decisions[8].

Investigator's Brochure:

Compilation of the current clinical and non-clinical information on the investigational medical device(s), relevant to the clinical investigation.

Investigator-Sponsored Trial:

Where an investigation is initiated by a clinician or a health care facility, not the device manufacturer, this is considered an investigator-sponsored trial. In this case, the data generated in the investigation are not intended to support a licence application or a new marketing claim. The funding for such research is typically provided by an independent third party, such as the CIHR (Canadian Institutes of Health Research). An investigator-sponsored trial may or may not require an ITA (see section 2.3.2 of this guidance).

Manufacturer-Sponsored Trial:

A clinical investigation initiated by the manufacturer, that involves either an unlicensed device, or a licensed device with unlicensed indications (see section 2.3.2 of this guidance). Usually, the manufacturer sponsors the trial for the purpose of marketing a new device for general sale, or for an already licensed device, for new indications.

Manufacturer:

Means a person who sells a medical device under their own name, or under a trade-mark, design, trade name or other name or mark owned or controlled by the person, and who is responsible for designing, manufacturing, assembling, processing, labelling, packaging, refurbishing or modifying the device, or for assigning to it a purpose, whether those tasks are performed by that person or on their behalf. An academic institution can meet the definition of manufacturer if the institution is the designer and/or owner of the device.

Medical Device:

Means a device within the meaning of the Act, but does not include any device that is intended for use in relation to animals.

Monitoring:

Act of overseeing the progress of a clinical investigation and to ensure that it is conducted, recorded, and reported in accordance with the Clinical Investigation Plan, written procedures, the International Standard (ISO), and the applicable regulatory requirements.

Objective:

Main purpose for conducting the clinical investigation.

Pre-ITA meeting:

A medical device manufacturer seeking to file an application to initiate a medical device investigational trial may request a meeting, either face-to-face or by teleconference, in order to address questions pertaining to Health Canada's investigational testing requirements for medical devices.

Principal Investigator:

Qualified person responsible for conducting the clinical investigation at an investigation site. If a clinical investigation is conducted by a team of individuals at an investigation site, the principal investigator is responsible for leading the team. Whether this is the responsibility of an individual or an institution can depend on provincial regulations.

Product Development:

Basic exploratory studies carried out to determine whether a test article has any potential utility.

Protocol:

A document that describes the objectives, design, methodology, statistical considerations and organization of a clinical trial (i.e., Clinical Investigational Plan).

Qualified Investigator:

Means a person who is a member in good standing of a professional association of persons entitled under the laws of a province to provide health care in the province and who is designated, by the ethics committee of the health care facility at which investigational testing is to be conducted, as the person to conduct the testing.

Randomization:

Process of assigning subjects to the investigational medical device or comparator groups using an established recognized statistical methodology to determine the assignment in order to reduce bias.

Risk Classification:

The classification of a medical device according to the Classification Rules set out in Schedule 1 of the Medical Devices Regulations.

Sell:

includes offer for sale, expose for sale, have in possession for sale and distribute, whether or not the distribution is made for consideration[9].

Serious Adverse Event:

Adverse event that:

a. led to death
b. led to serious deterioration in the health of the subject, that either resulted in
   i. a life-threatening illness or injury, or
   ii. a permanent impairment of a body structure or a body function, or
   iii. in-patient or prolonged hospitalization, or
   iv. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c. led to foetal distress, foetal death or a congenital abnormality or birth defect[10]

Significant Change:

Means a change that could reasonably be expected to affect the safety or effectiveness of a medical device. It includes a change to any of the following:

a. the manufacturing process, facility or equipment
b. the manufacturing quality control procedures, including the methods, tests or procedures used to control the quality, purity and sterility of the device or of the materials used in its manufacture
c. the design of the device, including its performance characteristics, principles of operation and specifications of materials, energy source, software or accessories; and
d. the intended use of the device, including any new or extended use, any addition or deletion of a contra-indication for the device, and any change to the period used to establish its expiry date[11]

Study Completion:

A study is considered complete after the last subject globally completes the "end of study" visit. The "end of study visit" is the final visit for study-related tests and procedures, including the capture of any final potential study-related adverse events. A study is not considered complete if the clinical trial is suspended, cancelled or closed.

Study Initiation:

The date when the investigation site will be ready to enroll patients in the study.

Subject:

Individual who participates in a clinical investigation. A subject can be either a healthy volunteer or a patient.

2.2 Pre-ITA application meeting

In most cases, general enquiries can be answered by email or by phone. In order to informatively and accurately respond to a sponsor's questions regarding an ITA application, and provide more in-depth advice, manufacturers and importers are encouraged to request a pre-ITA application meeting, particularly for novel Class III and IV devices and combination products. Such a consultation may be useful and can assist applicants with the completion of applications to facilitate a timely regulatory decision.

The purpose of these pre-ITA application meetings is to provide the manufacturer or importer an opportunity to present relevant data and discuss concerns and issues regarding product development. It also gives Health Canada an opportunity to provide guidance and highlight potential deficiencies or concerns with the proposed investigation. Manufacturers and importers may invite the qualified investigators who will be involved in the proposed investigation in Canada to attend the meeting.

2.2.1 Requesting a Pre-ITA application meeting

Requests for a consultation meeting or pre-ITA application meeting should be submitted in writing by the manufacturer or importer to the Investigational Testing Division of the Medical Devices Bureau at: hc.it-ee.sc@canada.ca.

Requests should be submitted in the form of a cover letter proposing three (3) dates and times suitable for the meeting. The cover letter should be accompanied by the following inf

- A synopsis of the proposed study;
- A list of preliminary questions to be addressed by Health Canada during the meeting; and,
- Sufficient information for Health Canada to assess the utility of the meeting and identify the appropriate staff necessary to discuss the proposed issues. This will assist in ensuring efficient use of Health Canada resources.

Health Canada will acknowledge the request for a meeting in a timely manner. If Health Canada agrees to hold the meeting, the acknowledgement will indicate the date that the pre-ITA application information package is to be provided, the meeting date and location, as well as the list of attendees. Please note that Health Canada reserves the right to propose a teleconference meeting or to address the questions by email correspondence, instead of a face-to-face meeting.

2.2.2 Information package for Pre-ITA application meetings

The information package should be submitted in electronic format, and should contain:

a. the proposed agenda, any prepared slides, including a finalized list of questions, and a complete list of attendees [it is recognized that the slides may change prior to the meeting];
b. a brief summary of applicable data including:
    i. a tabular listing of completed pre-clinical and clinical studies
    ii. the device specifications, preclinical testing, including the results of bench tests and animal studies
    iii. a list of the standards used in the design and manufacture of the device
    iv. the observed adverse events and a discussion of potential safety problems;
c. a proposed global clinical plan for the current stage of device development including regulatory status in other countries [it is recognized that this plan is subject to change as new information becomes available]; and,
d. details of the proposed clinical investigation to be conducted in Canada, within the scope of the intended ITA, including:
    i. a statement of trial protocol design
    ii. a study hypothesis and the objectives of the study
    iii. the condition to be treated or diagnosed, and a description of the treatments available
    iv. proposed procedures and/or criteria for patient monitoring, clinical effectiveness and safety endpoints to be assessed, along with any success/fail criteria
    v. statistical considerations.

Should the pre-ITA application package be found to be deficient, the manufacturer or importer may be requested to reschedule or postpone the meeting to allow the manufacturer or importer to assemble a more complete package. Please note that Health Canada reserves the right to modify or truncate the proposed agenda as it sees fit to better achieve the stated goals of the meeting.

2.2.3 Record of the Pre-ITA application meeting

The manufacturer or importer is responsible for sending Health Canada a written record of the discussion and conclusions of the meeting within fourteen (14) days after the meeting. All final records of this consultation will be kept on file.

A copy of the record of discussion and conclusions approved by all parties in attendance at the meeting should be included in the subsequent ITA application.

2.3 ITA applications

Under the Regulations, only manufacturers and importers can apply for an authorization to conduct investigational testing on human subjects in Canada. In either case a senior official of the manufacturer must complete and sign the Application Form (https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/forms/application-investigational-testing-authorization-forms-medical-devices.html). However, an investigator/clinician may act as a regulatory correspondent, if authorized by the manufacturer. Based on the requirements of section 82, supporting records as detailed in section 81 paragraphs (a) to (k) applicable to the device classification and section 86 (labelling) of the Regulations must be submitted. Health Canada expects that these records be submitted in an editable electronic copy[12].

2.3.1 Stages of product development

First in Human (FIH):

A first in human study is a type of study designed to evaluate a device for a specific indication for the first time in humans for the purpose of:

- gaining initial clinical insights
- refining device design
- addressing an unmet clinical need, or
- when additional non-clinical testing is not feasible

Early Feasibility:

An early feasibility study is a limited clinical investigation of a device early in development, typically before the device design has been finalized (e.g., innovative device for a new or established intended use or marketed device for a novel clinical application). Clinical investigation designed to obtain initial insights into the safety and performance of a new device.

Traditional Feasibility:

Clinical investigation designed to capture preliminary safety and effectiveness information on a near-final or final device design to adequately plan an appropriate pivotal study.

Pivotal Study:

Clinical investigation designed to collect definitive evidence of the safety and effectiveness of a device for a specified intended use, typically in a statistically justified number of subjects.

In general, as a sponsor proceeds through the stages of product development, more evidence in support of the use of the product for more specific clinical indications will be

gathered. For first in human and early feasibility studies, there may be an emphasis on pre-clinical/nonclinical testing and a thorough risk assessment compared to traditional feasibility and pivotal studies, where additional clinical data supportive of the proposed indications and patient population may be expected. However, this may also be case dependent and for this reason, it is difficult to outline specific criteria of data required for each of the above stages. Please consult our office for additional information concerning your specific case/circumstances.

2.3.2 When to apply for an ITA

2.3.2.1 Eligible studies

An ITA application is required for all unlicensed class II, III, and IV medical devices (as defined under the Food and Drugs Act) that will be imported and/or sold in Canada for the purpose of investigational testing involving humans (refer to Appendix 3), so that Health Canada can determine whether:

- the unlicensed device can be used clinically without seriously endangering the life, health or safety of patients, users or other persons;
- the study is not contrary to the best interests of patients; and,
- the testing objectives will be achieved.

The classification of a medical device product is based on the manufacturer's representation of the device in the labelling, and how it will be used in the study. Additional information to assist with classification can be found in the Guidance on the Risk-based Classification System for Non-In Vitro Diagnostic Devices (non-IVDDs) and the Guidance for Industry - Keyword Index to Assist Manufacturers in Verifying the Class of Medical Devices (refer to Appendix 2).

Manufacturers may contact the Investigational Testing division of Health Canada for additional guidance, and to determine whether an ITA application is required at: hc.it-ee.sc@canada.ca.

2.3.2.2 Non-eligible studies

An ITA is not required if there is no sale of the medical device, based on the definition of sale under the Food and Drugs Act. Consequently, if the development, manufacture, and testing of the device are conducted within a single corporate entity, no sale has occurred and the requirements of the Regulations do not apply. The testing must be limited to use on-site (at the corporate entity), and solely by the legal manufacturer.

An ITA is not required for the conduct of a study using a licensed device according to its licensed indications for use (whether it is manufacturer or clinician sponsored).

A licensed device to be used in a manufacturer-sponsored study intended to generate data to support a new indication for use will require an ITA application.

However, licensed medical devices used in clinician-sponsored investigations that are not initiated by the manufacturer, and are not intended to generate data to support a licensing application do not require an ITA. Likewise, licensed medical devices used in clinical investigations outside the scope of the authorized indications for use and not sponsored by the manufacturer do not fall under the Regulations; this is considered off-label use.

If the investigator initiated trial involves an unlicensed device, an ITA would be required. In these cases, the investigator must obtain the cooperation of the manufacturer, who must be the official applicant and signatory for the ITA application. Regulatory correspondence and clinical oversight can be delegated by the manufacturer who is the legal sponsor of the clinical investigation.

Parallel applications for an ITA and a medical device licence should not be submitted, where the ITA application is not intended to gather additional safety and/or effectiveness information to support a device licence, but instead is used to gain expedited market access.

2.3.2.3 WIP pulse sequences for magnetic resonance imaging devices

A pulse sequence is considered a component or accessory of a Magnetic Resonance Diagnostic Device (MRDD) system, which meets the definition of a Class II medical device. It is a software-based set of instructions that control how the device operates in order to capture images using variables such as echo time, repetition time, flip angle, field of view, resolution, pulse bandwidth, and post processing. Clinical studies involving work-in-progress (WIP) pulse sequence software protocols for MRDDs are often exchanged between manufacturers and researchers for the purpose of testing the WIP pulse sequence within the licensed MRI device parameters.

In the context of the regulatory review and for international alignment purposes, Health Canada has taken the position that investigators are no longer required to obtain approval from the department prior to starting a trial using a WIP pulse sequence when the conditions below are met. Before initiating a trial, investigators should:

- obtain REB approval, including patient informed consent (subsection 81(h) of the Medical Devices Regulations)
- ensure that the WIP pulse sequence is accompanied by clear instructions that state the WIP is not for diagnostic use, to guide treatment decisions, or to either mitigate or prevent disease
- ensure that the WIP does not introduce additional clinical hazards including but not limited to increased anesthetic use for pediatric patients, delays for critical care patients, or scanning of patients with MR-conditional implants
- ensure the trial will be conducted within the approved indications for use of the MRDD, and
- ensure the listed operating parameters below for main static magnetic field, specific absorption rate, gradient fields rate of change and sound pressure level are met

A pulse sequence operating outside the limits governed by the licensed MR scanner or use of a WIP with an unlicensed scanner would still require an ITA.

An investigator that is unsure if their trial meets these conditions is encouraged to contact Health Canada to determine whether an ITA is required.

WIPs which do not require an ITA must not exceed the following listed parameters:

Main static magnetic field

Population	Main static magnetic field greater than (tesla)
adults, children, and infants aged > 1 month	8
neonates i.e., infants aged 1 month or less	4

Specific absorption rate

Site	Dose	Time (min) Equal to or greater than:	SAR (w/kg)
whole body	averaged over	15	>4
head	averaged over	10	>3.2

Gradient fields rate of change

Any time there is a rate of change of gradient fields (dB/dt) sufficient to produce severe discomfort or painful nerve stimulation.

Sound pressure level

Peak unweighted sound pressure level greater than 140 dB, and a-weighted root mean square (rms) sound pressure level greater than 99 dBA with hearing protection in place.

2.3.3 Filing an ITA application

All applications must be submitted electronically in accordance with current format for the submission of ITA applications, as specified in the Notice - Applications for Investigational Testing Authorization (ITA), for Medical Devices, in the "Non-eCTD Electronics-Only" Format (refer to Appendix 4). You may also refer to the Guidance Document: Preparation of Regulatory Activities in "Non-eCTD Electronic-Only" Format for detailed guidance on filing medical device regulatory activities and subsequent transactions, in the "non-eCTD electronic-only" format (refer to Appendix 2). It should be noted that Health Canada no longer accepts paper copies of applications. Applications should be submitted by e-mail to hc.devicelicensing-homologationinstruments.sc@canada.ca, or sent by mail to the Health Canada mailing address (refer to Appendix 1) on a CD or DVD if it is too large to be sent by e-mail (20 MB). Applications sent by email should include a subject line that clearly distinguishes it as an ITA application. Requests for revised ITA applications should be clearly marked as such and include the previously assigned application number. ITA applications are not subject to a fee.

Applications sponsored by an investigator or a third party (e.g., a funding agency, a drug manufacturer, another device manufacturer, or a health care institution), must be signed by a senior official of the manufacturer of the unlicensed device. Regulatory correspondence and clinical oversight can be delegated to the clinical investigator, manufacturer, their regulatory agent, or contract research organization. In this case, the official who has delegated authority assumes the responsibilities for the importer to submit the application.

Manufacturers are encouraged to register their clinical investigations on a publicly accessible registry which accepts international clinical trial information and which is recognized by the World Health Organization (WHO). ClinicalTrials.gov (https://clinicaltrials.gov/) and Current Controlled Trials International Standard Randomised Controlled Trials Number Register (http://www.isrctn.com/) are acceptable. Information on investigational testing of medical devices in Canada can be obtained directly from the manufacturer, or by consulting one of the registries.

2.3.3.1 Multiple devices used in one study

In the case where one study protocol contains multiple unlicensed devices by different manufacturers, each manufacturer must submit a separate ITA application (form and submission). A manufacturer may only list the devices they manufacture on their application form. As an option, one manufacturer may submit a complete ITA application which contains all "Institutional Information" and "Study Documents" contents. These sections may be referenced in the other manufacturer(s) ITA application(s), however each manufacturer must still submit all device specific data and/or testing for the devices that they manufacture. The executive summary or cover letter should indicate the rationale for using the unlicensed device in conjunction with the other devices under the same study protocol as well as reference whether an application is pending or to be submitted for the other devices. To the extent possible the applications should be submitted at the same time. Authorization will not be granted until all applications have been submitted and found to satisfy the regulatory requirements.

2.3.3.2 Devices used in drug clinical trials (pharmaceuticals and biologics)

International drug clinical trials sometimes use ancillary devices that are not licensed in Canada. For Clinical Trial Applications (CTAs) that involve the use of an unlicensed Class II, III, or IV medical device, a separate ITA application and CTA must be filed and each should be authorized before the trial can commence in Canada. These applications can be filed concurrently.

In this case, the manufacturer of the device must sign the ITA application form, and regulatory correspondence is usually delegated to the drug sponsor. For Class III and IV devices, the pre-clinical information is submitted to Health Canada by the device manufacturer, and the study protocol and Informed Consent Forms (ICFs) are submitted by the sponsor of the drug study. Although the study protocol and the ICF are relevant to the pharmaceutical/biologic study, these documents should be filed for review with the corresponding ITA application. The CTA number should be provided at the time the ITA application is submitted (or as soon as it becomes available) as well as information on when it was submitted, and a No Objection Letter (NOL), if one has been issued.

2.3.3.3 Combination products and joint reviews

For the investigational testing of a drug/biologic-device combination product, ITAs or CTAs must be submitted to the lead Directorate within Health Canada, depending on the principal mechanism of action and hence the classification of the product. Refer to the guidance document entitled Drug/Medical Device Combination Products Policy (refer to Appendix 2).

Authorization for the sale and importation of all investigational products to be used within a medical device clinical investigation or a drug/biologic clinical trial must be obtained prior to the initiation of the clinical trial or implementation of the protocol amendment. Therefore, separate ITAs or CTAs (drug or biological) must be submitted for investigational products that are not regulated as combination product.

Health Canada will be responsible for communicating all regulatory decisions to the sponsor or manufacturer.

2.3.4 Organization of an ITA Application

To facilitate the timely evaluation of ITA applications, it is recommended that the manufacturer or importer provide a detailed cover letter, an executive summary, a table of contents and the required sections based on the class of the medical device to support the intent of the application. The application should be organized as outlined in Appendix 4.

For cases where multiple investigations are being conducted using the same medical device, a separate ITA application is required for each study protocol. When submitting an ITA for a new protocol using a previously authorized device and no changes have been made to the device since its last authorization, the device information in the new ITA application should be cross-referenced to the previous ITA application. In such cases, the cross-references should appear in the new ITA application package under the appropriate folder where the information would be expected to be found, and should include the ITA application number, date of information submitted, and section/folder number of the referenced previous ITA application. In all cases, when the device information from the previous ITA remains unchanged, a cross-reference should be used and the information should not be resubmitted.

When cross-referencing device information to a previous ITA where the investigation has been completed and closed, the results of the previously authorized study should be provided, if available at the time of submitting the ITA application.

Information in the document may be in either French or English. Material in a foreign language must be accompanied by an English or French translation.

The manufacturer or importer is responsible for informing Health Canada of changes in regulatory contact information. Changes to the assigned regulatory contact should be submitted by the current regulatory contact or a senior official in the company and addressed to: hc.devicelicensing-homologationinstruments.sc@canada.

2.3.5 Requirements of an ITA application

Information that must be submitted for an ITA application depends on the risk class of the device and is outlined in Table 1. The manufacturer or importer must possess records that contain all of the information and documents required under section 81 of the Regulations. For some Class II devices, Health Canada may, under section 84, request additional inf

is normally required for a Class III or IV device. It should be noted that the evidence required to demonstrate safety, effectiveness, or performance for devices to be used in investigational testing is different from the evidence required for a licence application.

Applications must meet all regulatory requirements, have a favourable benefit to risk ratio, and address potential risks in a complete patient ICF.

Manufacturers should follow the principles of the Declaration of Helsinki and the Tri-Council Policy Statement (2nd Edition): Ethical Conduct for Research Involving Humans (2014), and conform to Good Clinical Practices (GCP) as set out by ISO 14155 - Clinical investigation of medical devices for human subjects. ISO 14155 is generally consistent with the definitions and requirements of the Regulations. Where inconsistencies exist, the Regulations take precedence.

Conformity with GLP is strongly recommended, and animal studies should be conducted with scientific rigour similar to that in human trials.

Applications for devices that were previously authorized for investigation under a different study protocol can be cross-referenced for device specific information. The results of the previously authorized study should be provided, if available at the time the application is submitted.

Table 1 lists ITA application requirements for different device classes.

Table 1 – ITA application requirements for different device classes

Requirements for an Investigational Testing Authorization (ITA)	
Class I	There is no requirement to obtain an ITA for a Class I medical device. Subsection 80(3) of the Regulations permits a manufacturer or importer of a Class I medical device to sell the device to a qualified investigator for the purpose of conducting investigational testing. The manufacturer or importer is still required to possess all the records and information detailed in section 81. Institutional requirements and Research Ethics Board (REB) approval apply.
Class II	The information required under subsections 81(a), (b), (h), (i), and (j) must be submitted. The manufacturer or importer must possess records that contain all the information required by section 81 of the Regulations. It is not required that evidence of REB approval is provided to Health Canada, but it must be obtained prior to study initiation, in accordance with institutional policies.
Class III and IV	The information required under subsections 81 (a) to (k) must be submitted. However, a "Letter of Authorization" for investigational testing may be issued, prior to the receipt of REB approval and finalization of the qualified investigators and investigational sites, provided that the name and accompanying information (name, address, cv, and signed attestation) of at least one qualified investigator at one investigational site is identified at the time of filing.

Contents of the Application Package	
Class II, III and IV	**Cover Letter & Executive Summary** Include a short Cover Letter to explain the reason for the application and indicating the applicant's name, any cross-references to previous ITAs and/or device licences, as well as whether the application is a new or revised ITA (with a reference to the ITA number). In addition, a one or two page Executive Summary of the application should be submitted (refer to Appendix 4).
	Table of Contents Include a Table of Contents listing the contents of the application and their location.
	Application Form Include a copy of the completed ITA Application form (Application for Investigational Testing Authorization, refer to Appendix 2).
	Pre-submission Correspondence Include copies of any decisions from pre-submission correspondence that occurred with Health Canada, including minutes from pre-ITA meetings, application enquiries, classification decisions, as well as correspondence with other bureaus in Health Canada.
Introduction	
Class II, III and IV **Subsection 81(a)**	**Manufacturer or Importer Identification** Provide the complete name and address of the device manufacturer and importer, if applicable, including contact names, e-mail addresses, fax and telephone numbers. The name of the legal manufacturer must be consistent with the information found on the device labelling.
Class II, III and IV **Subsection 81(b)**	**Device Identification** Provide the name of the device and the device identifiers, as they appear on the label. This includes any component, part or accessory that is part of the device. Specify the risk classification of the device based on the Classification Rules set out in Schedule 1 of the Medical Devices Regulations and on the manufacturer's representation in the labelling. For assistance in determining the risk class please refer to the Guidance on the Risk-based Classification System for Non-In Vitro Diagnostic Devices (non-IVDDs) and the Guidance for Industry- Keyword Index to Assist Manufacturers in Verifying the Class of Medical Devices. If, after reviewing these documents assistance is still required you may contact, hc.mdb.enquiries-enquetes.bmm.sc@canada.ca.

	To confirm the risk classification of the device, copies of device labelling with clear descriptions of the device and an intended use/indications for use statement can be submitted to the Device Licensing Services Division at, hc.devicelicensing-homologationinstruments.sc@canada.ca. The risk classification of a device under investigational testing may differ from that of the device in general sale if, for example, a new indication is being investigated. The risk class assigned to an investigational device may also be different from the classification assigned by Health Canada at the time a future license application is filed if at the time of licensing it is deemed to present a higher or lower risk. This section should also include the number of units of each individually sold device requested for the conduct of this study in Canada (including the total number of devices used and estimates of the number of devices per site).
Class III and IV **Subsection 81(c)**	**Device Description** This section requires a complete description of the device, hardware and software components, and materials used in its construction and packaging (i.e., physical and chemical characterization, key specifications and performance features, component parts, accessories, patient contact materials, and packaging materials). This description should include good quality colour photographs of the device, its components, parts and accessories and engineering diagrams, where appropriate. Engineering diagrams of long term implantable devices aid in the determination of dimensions and relative proportions. These should be provided with an original application for investigational testing. Engineering diagrams for other device types, such as electro-medical devices may be requested as additional information if necessary to establish the safety and potential effectiveness of the device in question. If the device has previously been authorized for investigational testing or granted a medical device licence, provide the authorization number and clearly specify if changes have been made to the device. If so, provide a tabular comparison of the similarities and differences with regard to the intended use, design, key specifications and performance features, hardware, software, accessories, patient contact materials, etc. It is recommended that this comparison be provided in tabular form.
Class III and IV **Subsection 81(d)**	**Design Philosophy** Include a description of the features of the device that permit it to be used for the medical conditions and purposes for which it will be sold by the manufacturer. A brief description of the device's design philosophy and performance specifications should be provided and linked to the objectives of the proposed investigational testing. References and comparisons with appropriate previous versions or generations of the device should be

	presented. A tabular format is preferred for this comparison. This section should include an overview of the purposes and principles of operation for the device and should include a summary of the method of use and operation of the device.
Class II, III and IV **Subsection 81(d)**	**Indications for Use, Intended Use, Contraindications** Include the proposed indications for use and/or intended use as well as any contraindications for the device, as proposed by the manufacturer.
Class III and IV **Subsection 81(e)**	**Marketing History** The marketing history should provide details of the regulatory status of the device in other jurisdictions, the volume of sales by country, a summary of reported problems with the device and details of any recalls in other jurisdictions. Include a summary of Special Access requests made to Health Canada and the outcome of these requests.
Risk Assessment and Risk Reduction Measures	
Class III and IV **Subsection 81(f)**	**Risk Assessment** The risk assessment is an analysis and evaluation of the risks inherent in the use of the device and the measures adopted to reduce these risks to acceptable levels for the purposes of conducting the investigational testing. The use of ISO 14971-1 (Medical Devices - risk management Part 1: Application of risk analysis) is recommended. Include a list of all possible hazards and evaluate them against the presumed benefits of the device. Additionally, an indication of the way by which the risks have been reduced to acceptable levels must be provided. The risk analysis should be signed, and the identity of the responsible individual provided.
Class II, III and IV **Subsection 81(f)(i)**	**Previous Studies** The results of any previous research, bench testing, pre-clinical and clinical studies conducted with the device must be provided. These results are useful in assessing the safety and potential preliminary effectiveness of the device for investigational testing. Examples include physical and mechanical bench testing, biological safety, electrical safety, software validation and verification, biocompatibility, shelf life, sterilization validation and residuals testing, packaging validation, animal studies and clinical studies. Supporting literature and a bibliography should be provided, as applicable. Evidence of conformity to recognized standards should be provided, as described in the Guidance Document: Recognition and Use of Standards under the Medical Devices Regulations (refer to Appendix 2). A Declarati

	Conformity (DoC) to a recognized standard can replace detailed pre-market information to satisfy the regulatory requirements. It should be noted that if conformity is declared to a standard that specifies only test methods (such as ISO 10993 for the evaluation of biocompatibility), or procedures (such as ISO 14971 for application of a risk management system for medical devices), quantitative information on test results is also required. In the case of Class II devices, a DoC is usually adequate to initially support safety of the device. However, Health Canada reserves the right to request additional information on a case by case basis.
Class III and IV **Subsection 81(f)(ii)**	**Alternate Treatments** Provide a description of the methods currently used to diagnose or treat the medical conditions that are the subject of the proposed investigational testing.
Class III and IV **Subsection 81(f)(iii)**	**Precautions** Provide information respecting any cautions, warnings, contra-indications and possible adverse effects associated with the use of the device.
Class II, III and IV **Subsection 81(g, h)**	**Institutional Information** For Class II devices, provide the full name of the investigator(s) as well as the name and full mailing address and primary contact information of each institution where the testing is proposed to be conducted. Investigators who are not actively involved in the implantation or use of the device should not be listed. These institutions and names of the investigators actively involved in the implantation or use of the device will be listed on the authorization specified under subsection 83(2). In addition, for class III and IV devices the curriculum vitae should be provided for each investigator to be included on the authorization letter. A "Letter of Authorization" for investigational testing may be issued, even if the institutions and names of qualified investigators are not all known at the time of submitting the ITA application. At a minimum, information on at least one of the qualified investigators and investigational sites is required at the time of filing. Additional investigators and sites can be added to the authorization by filing the form, titled "Application for Revised Investigational Testing Authorization". Please submit the form to, hc.devicelicensing-homologationinstruments.sc@canada.ca.
Class III and IV **Subsection 81(h)**	**Research Ethics Board Approval** For Class II medical devices, although REB approval must be obtained before study initiation, applicants are not required to provide evidence of written approval from the REB to Health Canada (refer to Appendix 5).

	For Class III and IV medical devices, applicants are required to provide evidence of written approval from the REB along with study documents referenced in the REB approval to Health Canada prior to study initiation. This approval letter must reference the most current study documents (e.g. protocol and informed consent forms). REB approval should ideally be submitted with the ITA application. However, Health Canada may issue a "Letter of Authorization" for investigational testing, if the application meets the requirements stated in Part 3 of the Regulations and REB approval is not available at the time the ITA application review has been completed. Prior to study initiation, written REB approval which references the most current study documents must be submitted to hc.devicelicensing-homologationinstruments.sc@canada.ca. If REB approval references updated study documents, you must submit the following prior to study initiation: 1. a completed form titled "Application for Revised Investigational Testing Authorization"; and 2. updated red-lined and clean copies of the protocol and ICF document versions referenced in the REB approval. Please note that red-lined versions must show all changes made from the Health Canada approved version. If the protocol or ICF versions referenced in the REB do not differ from those indicated in the Letter of Authorization, the REB may be submitted to Health Canada without completing an application form. The information on the REB approval will be verified, and an acknowledgement of receipt will be sent. A description of the constitution, roles, and responsibilities of an REB can be found under the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2) and ISO 14155. Please note that previous REB refusals (Canadian and foreign) should be reported and discussed in your initial application.
Class II, III and IV **Subsection 81(i)**	**Protocol** A protocol in line with the GCP recommendations, as per ISO 14155, should be provided. The protocol should include a version number and date of last modification, for document control purposes. The protocol of the proposed investigational testing should contain the following information, in easily identifiable subsections. Background information describing the disease or condition to be treated, prevalence, diagnostic criteria, and current treatment, study hypothesis, study objectives, study design, inclusion and exclusion criteria, number of devices and study subjects required, as well as detailed information on the duration of the investigation and the follow-up period for patients. The methods of assessing the investigational device must be ful

	including the criteria for success or failure of the performance of the device. Provide a copy of all case report forms to be used in the investigation. The proposed methods of data analysis should be described, including the identity of the person or group performing the analysis. Methods of data quality control should be specified. The control group must be fully described, and a justification provided for the type of control group chosen. Provide a full description of the subject selection, including: • the number of Canadian subjects (by institution), including a justification for the proposed number; • inclusion and exclusion criteria, including the participants' ages, sex and diagnosis of primary and secondary (if applicable) conditions; and • the diagnostic method(s) chosen to confirm the disease or condition. Subjects should be selected to be representative of the population intended to be treated with the device, with appropriate inclusion of children, women, and ethnic groups. Specify the estimated time frame for the conduct of the study, including the duration of the enrolment phase, the duration of the treatment phase, and the duration of the follow-up phase. Also include the approximate duration from the start of enrolment to the end of follow-up period. This can be provided as part of the protocol or provided separately. **Investigator's Brochure (IB)** A copy of the current IB should be submitted for high risk class III and IV devices. This should be supplemented as appropriate with up-to-date safety, non-clinical and clinical data. The IB containing all information regarding the product to date should be prepared in accordance with ISO 14155. **Informed Consent Form (ICF)** Include a copy of the ICFs to be used in conjunction with the study, including information regarding the risks and anticipated benefits to the patients as a result of their participation in the investigational testing. The ICFs to be used in conjunction with the study should be prepared in accordance with applicable laws governing consent. ISO 14155 and the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2) provide requirements for the ICF. The document should include a version number and date of last modification (for document control purposes) which must be referenced by the most current and relevant REB approval.
Class II, III and IV **Subsection 81(j)**	**Device Labelling** The labelling requirements are described in section 86 of the Regulations. In addition to the name of the device and the name of the manufacturer, the label must include the statements "Investigational Device" and "To be Used by Qualified Investigators Only" and "Instrument de recherche" and "Réservé uniquement à l'usage de chercheurs compétents" in English and

	possible to use alternate phrasing, provided the above meanings are conveyed. This should be included in the Operator's Manual (or Instructions for Use) and on the package label. For reusable devices, such as capital equipment, a label should be put directly on the device and/or the displayed on the start-up screen of the graphical user interface. The device label must be in either English or French. This includes the device package labels, outer carton labels, Instructions for Use (IFU), Operator's Manual, Training Manual, and all advertising brochures intended to be used with the device. Where the directions for use are supplied in only one official language at the time of sale, directions for use in the other official language must be made available by the manufacturer as soon as possible at the request of the purchaser. For RCTs, the required labelling (device name, manufacturer name, investigational statement) must be affixed to the outer container, and each individual device (study and control) must bear an assigned code, the manufacturer's name, and the investigational use statement in French and English. The intent of this label is to ensure that the device is not used other than under the study protocol.
Class III and IV **Subsection 81(k)**	**Investigator Agreement(s)** A signed investigator agreement is required for each investigator to be listed on the authorization. This agreement outlines the responsibilities of the investigator to: • conduct the testing in accordance with the protocol • fully inform each enrolled patient • not permit the device to be used outside the agreed protocol • supervise the use of the device, and • report all incidents under section 59 to the Minister within 72 hours A template of an investigator agreement form is available on the Government of Canada website (refer to Appendix 2). An alternate format is acceptable provided the five (5) conditions described in subsection 81(k) are adequately addressed. Manufacturers and importers are reminded that at least one qualified investigator along with their investigator agreement is required at the time of filing the ITA. The new form, titled "Application for Revised Investigational Testing Authorization" should be provided to Health Canada for revisions made to study investigators, sites or their agreements, soon as the information becomes available post-initial authorization. Such revisions can be submitted via this form to, hc.devicelicensing-homologationinstruments.sc@canada.ca.

Additional Considerations	
Class II, III and IV	**Minimizing Bias** Bias should be minimized by adherence to currently accepted standards of protocol design as described in the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2) and ISO 14155.
	Inclusion of women, children, and vulnerable populations Efforts should be made to maximize compliance with the International Council for Harmonisation (ICH) Document E11 entitled Clinical Investigation of Medicinal Products in the Paediatric Population and the Health Canada Guidance Document: Considerations for Inclusion of Women in Clinical Trials and Analysis of Sex Differences (refer to Appendix 2).
	Clinical Trial Design and Statistical Considerations The clinical trial design will depend on the stage of development of the device and the clinical investigation. Blinding (Masking) and Randomization are particularly important for reducing bias in pivotal studies. A comparator arm is recommended whenever feasible. This includes trial designs in which subjects serve as their own control, either concurrently (e.g., split face therapy) or sequentially. The statistical basis of the study will be considered to ensure that "the objectives of the study will be achieved" under subsection (83(1)(c)). General guidance on this topic can be found in the ICH documents E8: General Considerations for Clinical Trials, E9: Statistical Principles of Clinical Trials, and E10 Choice of Control Group and Related Issues in Clinical Trials and Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2) (refer to Appendix 2).

2.3.6 The investigational testing authorization

Health Canada will issue an authorization under section 83 of the Regulations after a review of the submitted information is deemed to satisfy the requirements of the Regulations.

This letter will be the manufacturer's legal authorization to import and sell the requisite number of devices to the investigators or institutions listed under the Authorization for use in the referenced study protocol.

The Letter of Authorization will specify the name of the device, the study protocol title, date and version number, the date of the ICF, the objectives of the study, the authorized number of devices to be imported and sold and number of study subjects to be recruited in Canada, as well as the names of the investigators and institutions where testing may be conducted. This information, along with REB approval(s), is required prior to study initiation. Refer to section 2.3.5 for further details.

2.4 Responsibilities of manufacturers and importers

2.4.1 Advertising

Section 87 of the Regulations prohibits advertising a medical device that is the subject of investigational testing unless an authorization has been issued, and the advertisement clearly indicates that the device is the subject of investigational testing, and the purpose of the clinical investigation.

2.4.2 Quality management system

It is expected that manufacturers will have implemented a proper quality management system. Evidence of certification to ISO 13485 is not a requirement for an ITA, however it may be used as guidance.

2.4.3 Record keeping

Under section 80 of the Regulations, the manufacturer or importer of a medical device undergoing investigational testing in Canada must maintain records as detailed under section 81 of the Regulations. The Regulations do not cover the document retention period for clinical institutions. This period should be in line with institutional policies and provincial regulating bodies for the practice of medicine[13].

2.4.4 Distribution records

Under section 88 of the Regulations the manufacturer, importer and distributor of a medical device undergoing investigational testing in Canada must maintain distribution records as detailed under sections 52 to 56.

2.4.5 Mandatory problem reporting

The qualified investigator is required to report serious adverse events to Health Canada and to the manufacturer and importer within 72 hours of discovery. This includes cases in which the incident:

a. is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labelling or in its directions for use, and
b. has led to the death or a serious deterioration in the state of health of a patient, user or other person, or could do so were it to recur

For an incident that occurs in Canada, the manufacturers and importers are required to provide a preliminary and a final report in respect of the incident. The preliminary report shall be submitted:

i. within 10 days after the manufacturer or importer of a medical device becomes aware of an incident, if the incident has led to the death or a serious deterioration in the state of health of a patient, user or other person, or

ii. within 30 days after the manufacturer or importer of a medical device becomes aware of an incident, if the incident has not led to the death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur.

Further details for the information required in the reports, as well as reporting for incidents outside of Canada can be found in sections 59 to 62 of the Regulations. Manufactur

reference the Guidance Document for Mandatory Problem Reporting for Medical Devices and relevant forms (refer to Appendix 2) for the process of submitting these reports. Health Canada does not currently have a mandatory form specifically for healthcare professionals. In the interim, healthcare professionals can submit their ITA incidents through Health Canada's website. A copy of the Medical Devices Problem Report Form can be obtained at the following: https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement.html.

2.4.6 Other obligations

Manufacturers and importers must have documented procedures in place to handle product complaints and recalls as required by sections 57 and 58, and 63 to 65 of the Regulations. In addition, the appropriate records of these activities must be maintained.

For additional information, consult the guidance document on complaint handling and recalls (Recall Policy, refer to Appendix 2).

The manufacturer's responsibilities for implant registration, as described in sections 66 to 68, are also applicable (as appropriate) to devices authorized for investigational testing. Implant Registration cards are required for the devices listed under Schedule 2 of the Regulations.

2.5 Requests for revisions to an ITA

Manufacturers or importers may submit a request for a revised authorization to address changes made to the device, study investigation plan, or institutional information, such as those listed below:

a. A change to the device
   - A change involving modifications to device design (where the device generally maintains its original functionality and intended use), sterilization, software, materials, and/or labelling
   - A change in device name or device identifier
   - A change to the number of devices requested
   - A change to the manufacturer name

b. A change to the study documents (protocol and ICF)
   - A change to the study protocol that will not bias the data previously collected (see list of examples below)
   - ICF revisions (clarifications to language/wording)
   - Additional study subjects
   - Change to duration of study

c. A change to the institutional information
   - Addition or removal of institutions where the testing is being conducted
   - Change to the list of qualified investigator(s)
   - Updated REB approval information

Examples of protocol changes that would require a revised authorization are listed below. When in doubt whether an application is required, sponsors should contact the Investigational Testing Division at: hc.it-ee.sc@canada.ca.

1. Protocol revisions to permit the enrolment of additional study subjects and longer term patient follow-up.
2. Any protocol amendment that requires REB approval will also require a Health Canada authorization.
3. Inclusion and exclusion criteria modifications. These include changes to eligibility criteria, tests or procedures for selecting the study population, as well as tests, procedures, or criteria for dismissing clinical trial subjects prematurely or at the end of the trial.
4. Changes to the patient selection criteria, tests or procedures required for the ongoing assessment of clinical trial subjects, including assessment of safety, or evaluation of safety and effectiveness. This includes protocol changes as a result of serious unexpected adverse reactions.
5. Inclusion of sub-studies.
6. Changes to sample size estimation or addition of interim analyses that will affect the analysis and interpretation of the study results.
7. Changes to the post-treatment follow-up period that may affect the safety evaluation of the device.
8. Use of ancillary medical devices for the treatment or monitoring of the study subjects that may have an impact on the analysis of effectiveness or increase the risk to clinical trial subjects.
9. Changes to the requirements or procedure for reporting of serious, unexpected adverse reactions.

The criteria for issuing a revised authorization are:

- the changes do not have a major impact on the risk analysis originally submitted with the application
- the rights and safety or welfare of the study subjects are ensured
- the integrity of the study data collected to date is secure
- the scientific soundness of the plan is intact, and
- there are no changes to the overall study hypothesis or objectives

A new application is required for substantial study and/or device changes (e.g., new protocol that may bias the data, device design change that alters its functionality, new or changed indications for use) that introduce new risks. The submission of a new ITA application for this purpose requires the cancellation of the current authorization.

2.5.1 Filing requests for revisions to an ITA

All requirements for filing an ITA, as discussed in section 2.3.5 of this guidance document, are applicable to ITA revision requests, with the exception of the REB approval letter (see page 26). All applicable review sections that have changed as a result of the modifications or are required to validate the modified device and/or support its continued safety in the investigation should be re-submitted. Include a cover letter clearly distinguishing what aspects are modified and which remain unchanged, as well as what supporting information has been provided.

If the protocol, ICF, or labelling have been revised, both clean and redlined copies of the modified documents should be provided along with a tabular list of changes, and a rationale that supports each change.

If device changes are being made or new devices are being added, applicable verification and validation studies should be provided (e.g., design, electrical, performance, sterilization, biocompatibility, etc.).

When filing an ITA revision request, an ITA application form is only required if changes have been made to the device details (i.e., device names, catalogue number, addition/deletion of a device) on the letter of authorization. A new copy of the application form is required with a revised section 11 to reflect the changes, and should be signed by the manufacturer.

Applications for revisions to previously authorized ITAs should be submitted in electronic format following the structure under Appendix 4. All correspondence should reference the previously issued ITA number, including the email subject line and Cover Letter. Completed applications are to be submitted electronically in accordance with the current policy for the submission of ITA applications to: hc.devicelicensing-homologationinstruments.sc@canada.ca or by mail to Health Canada's postal address (refer to Appendix 1).

2.5.2 Additional information to be added to the file

Modifications made to the device or the investigation that are not deemed to be changes outlined in section 2.5, which are deemed significant for a revision, should also be reported to Health Canada. These changes will be acknowledged in writing, and a revised authorization may or may not be required depending on the nature of the proposed changes.

These changes may be submitted to Health Canada in the form of a Notification, following the "non-eCTD electronic only" format discussed in section 2.3.3. A detailed cover letter describing the change must be included. All applicable folders with modified information must also be included.

2.6 Cancellation of an ITA

Section 85 of the Regulations allows the Minister to cancel an ITA for Class II, III or IV devices, and to stop the sale of a Class I device that has been sold for investigational purposes, as outlined in subsection 85(1) paragraphs (a) to (e) when:

a. the testing seriously endangers the life, health or safety of patients, users or other persons,
b. the testing is contrary to the best interests of patients on whom the testing is being conducted,
c. the objective of the testing will not be achieved,
d. the qualified investigator who is conducting the testing is not respecting the undertaking required by paragraph 81(*k*), or
e. the information submitted in respect of the testing is false or misleading.

Prior to cancelling an ITA, Health Canada will request information from the manufacturer or importer to substantiate that the conditions set out in subsection 83(1) are still being met. If this information is not submitted, or if it is submitted and a review of the information determines that any of the conditions set out under section 83 are not met and/or any of the conditions set out under subsection 85(1) exist, the authorization will be cancelled by written notice outlining the reasons for the cancellation.

2.7 Review process for ITA applications and revisions to ITAs

2.7.1 Screening

New ITA applications are screened for administrative and scientific content to ensure that the applicable regulatory requirements of sections 81 and 86 of the Regulations have been addressed. A Screening Acceptance Letter is issued if the information is complete. If regulatory deficiencies are identified at screening, a Screening Deficiency Letter is issued which details the deficiencies. The manufacturer or importer is given fifteen (15) calendar days to provide the missing information, after which time the application is rejected (refer to the Policy on Management of Applications for Medical Device Licences and Investigational Testing Authorizations, Appendix 2). The response should include an Executive Summary listing the responses in a question and answer format, as well as all other documents in the appropriate section of the electronic folder structure for ITA applications (refer to Appendix 4).

2.7.1.1 Screening rejection letter

A Screening Rejection Letter is issued for grossly deficient applications, such as when substantial information which is required under section 81 of the Regulations is missing from the application. This may result from the submission of a Class II application for a medical device determined by Health Canada to be Class III or IV.

A Screening Rejection Letter will also be issued if the manufacturer or importer fails to provide the records required under section 81 within fifteen (15) days of receipt of a Screening Deficiency Letter that will specify the list of deficiencies. If an application is rejected, the applicant will be required to submit a new application with all relevant supporting data; cross-referencing a previously rejected application in a new application is not permitted.

2.7.2 Review

Once the review has been initiated un-solicited information should not be provided without consent from the Investigational Testing Division Manager. The review period for new ITA applications or requests for revised ITAs, other than for combination products, is thirty (30) calendar days from when screening is initiated. If a Screening Deficiency Letter was issued, the thirty (30) day review period begins on the day that Health Canada was in receipt of a complete and reviewable application. For minor administrative revisions (e.g., as outlined in section 2.5 of this guidance) to ITAs, the review period is fifteen (15) calendar days. It should be noted that these are estimated review targets and not default deadlines that result in automatic authorization.

After the review has been completed Health Canada may send a request for additional information as described in section 84 of the Regulations for any missing information required under section 81. The applicant must submit a complete response within sixty (60) calendar days. Upon receipt of the response to the additional information request from the manufacturer or importer, a new thirty (30) calendar day review period will begin.

Should the applicant be unable to provide the requested information within this timeframe, the application may be withdrawn and resubmitted without prejudice within six (6) months. After this time period a new application must be filed. Requests for additional information that have

not been responded to within sixty (60) days will be subject to a refusal. Extensions for additional information may be granted on a case-by-case basis.

If the information submitted in support of the ITA or ITA revision is deemed to be satisfactory, Health Canada will issue an authorization or revised authorization.

2.7.2.1 Refusal of an application

The ITA application or revised application may be refused if it is determined that:

- the device cannot be used safely for investigational testing
- the investigational testing is contrary to the best interests of patients
- the evidence does not demonstrate that the stated objective of the testing can be achieved, or
- the records required under section 81 and section 86 have not been provided

A Refusal letter will be issued itemizing any and/or all deficiencies.

The manufacturer or importer may appeal a refusal to issue an ITA. Information on the appeal process for decisions made regarding investigational testing applications can be found in the document Management of Applications for Medical Device Licences and Investigational Testing Authorizations (refer to Appendix 2).

2.8 Post-authorization requirements

2.8.1 Discontinuation of the investigational testing

In the event of the premature discontinuation of a study in its entirety or at a study site for which an ITA or ITA revision has been issued in Canada, the manufacturer or importer should notify Health Canada as soon as possible, but no later than fifteen (15) calendar days after the date of discontinuation.

This notification should include:

a. Detailed reasons for discontinuation, including whether it is related to the safety and/or effectiveness of the medical device.
b. Description of the impact of the discontinuation on the proposed or ongoing study conducted in Canada.
c. Confirmation that all investigators have been notified in writing of the discontinuation along with reasons, and that any potential risks to the health of the research subjects or other persons are clearly identified and described.
d. Confirmation that the sale or importation of the device to all discontinued sites has been stopped, and
e. Confirmation that the manufacturer will take reasonable measures to ensure the return of all unused devices.

Note: Notification of a premature discontinuation of international sites (due to safety reasons) for which there are ongoing studies with the medical device in Canada, should also be submitted to Health Canada.

2.8.2 Resumption of investigational testing

The manufacturer may resume the investigational testing in its entirety or at a site that was previously discontinued if the manufacturer submits the following information:

a. The name, address and telephone number, and electronic mail address of the qualified investigator for each site and of the REB that approved the re-initiation of the investigational testing at each site.
b. The name, address and telephone number and, if applicable, the fax number and electronic mail address of any REB that has previously refused to approve the re-initiation of the investigational testing, if applicable, and
c. The proposed date of re-initiation of the investigational testing at each study site.

Note: The above information may be submitted as Additional Information and Health Canada will provide acknowledgement of the resumption. When there has been a change to the device, the study protocol or the manufacturing process, the information should be submitted as a request for a revised ITA (refer to section 2.5 of this guidance). The study may resume only when a revised Letter of Authorization has been issued.

2.8.3 Study completion and site closures

Manufacturers and importers are urged to report the completion of the study to Health Canada. Inclusion of a final study report is encouraged (see section 2.8.4 of this guidance). Subsequent to this notification, Health Canada will issue a letter to confirm closure of the study. ISO 14155 provides additional guidance.

After completion of the investigational testing, re-usable devices, such as capital equipment, which are not yet licensed, should be returned to the manufacturer or importer. If the qualified investigator intends to use these devices under a different study protocol, a new application for investigational testing signed by a senior official of the manufacturer must be submitted. Clinical use of unlicensed medical devices other than under an authorised clinical protocol is prohibited.

2.8.4 Investigational testing report

After closure of the investigational testing, the manufacturer or importer should submit a report of the study to Health Canada even if the investigation was terminated prematurely.

a. The report should include identification of the device, a description of the methodology and design of the investigation, any deviations from the protocol, data analysis together with any statistics and a critical appraisal of the aims of the investigation.
b. The report should take into account the data from each investigation site and for all subjects. No subjects should be identifiable either from the investigation report or the published results.
c. Where applicable, the investigation testing report should be made available to the principal investigator and all investigators for review and comment. The sponsor shall maintain records confirming that the report has been provided for review. If a reviewer does not agree with all or part of the report, their comments should be recorded and communicated to the other principal investigators.

d. The sponsor and coordinating investigator should provide their signatures, indicating their agreement with the content of the report. If no coordinating investigator is appointed, the signature of the principal investigators should be obtained.
e. The report should be provided to the REB.

2.8.5 Public release of information about ITAs

Upon request, or when determined appropriate, Health Canada will publically release certain information about issued ITAs. The primary goal is to provide transparency and improve public access to information on Canadian studies involving medical devices. For ITAs authorized since November 14, 2013 the following information will be released:

- protocol title
- device name
- medical condition
- study population
- authorization date
- end date of the study, and
- name of the manufacturer or importer

For all other information enquirers will be redirected to the manufacturer or importer, or referred to their health care provider.

Appendix 1 - Relevant addresses

Medical Devices

Medical Devices Bureau
Therapeutic Products Directorate
Health Products and Food Branch
Health Canada
2nd Floor, 11 Holland Avenue, Tower A
Address Locator: 3002A
Ottawa, Ontario
Canada
K1A 0K9

General Enquiries concerning Investigational Testing:

E-mail: hc.it-ee.sc@canada.ca
Telephone: 613-941-8910

Pharmaceutical Drugs

Office of Clinical Trials
Therapeutic Products Directorate
Health Products and Food Branch
Health Canada
5th Floor, Holland Cross, Tower B
Address Locator: 3105A
1600 Scott Street
Ottawa, Ontario
Canada
K1A 0K9

General Enquiries:

E-mail: hc.oct_bec_enquiries.sc@canada.ca
Telephone: 613-941-2132

Appendix 2 - Useful documents

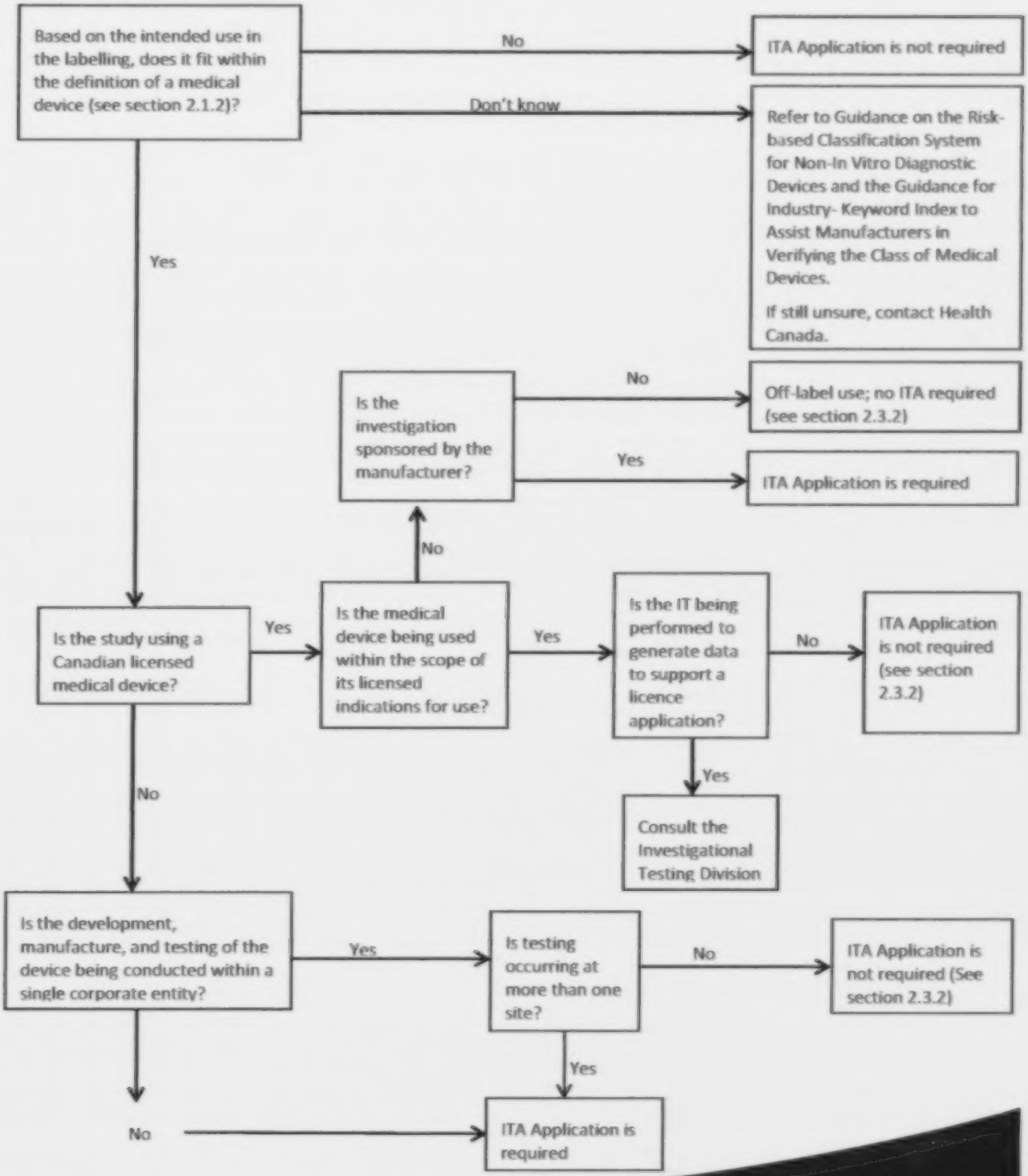
The following documents may be useful in the preparation of the application:

- Drug/Medical Device Combination Products Policy [2005-11-30] (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/policies/drug-medical-device-combination-products.html)
- General Considerations for Clinical Trials ICH Topic E8 [1998-05-01] (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/efficacy/general-considerations-clinical-trials-topic.html)
- Guidance Document: Considerations for Inclusion of Women in Clinical Trials and Analysis of Sex Differences [2013-05-29] (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/considerations-inclusion-women-clinical-trials-analysis-data-sex-differences.html)
- Guidance Document - E10: Choice of Control Group and Related Issues in Clinical Trials [2011-07-04] (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/efficacy/choice-control-group-related-issues-clinical-trials-topic.html)
- Guidance Document for Mandatory Problem Reporting for Medical Devices [2011-10-03] (https://www.canada.ca/en/health-canada/services/drugs-health-products/reports-publications/medeffect-canada/guidance-document-mandatory-problem-reporting-medical-devices-health-canada-2011.html)
- Guidance Document: Preparation of Regulatory Activities in the "Non-eCTD Electronic-Only" Format [2016-10-31] (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/common-technical-document/updated-guidance-document-preparation-regulatory-activities-non-ectd-electronic-only-format.html)
- Guidance Document: Recognition and Use of Standards under the Medical Devices Regulations [2006-09-22] (https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/guidance-documents/guidance-document-recognition-use-standards-under-medical-devices-regulations.html)
- Guidance for the Interpretation of Significant Change of a Medical Device [2011-01-20] (https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/guidance-documents/guidance-document-interpretation-significant-change-medical-device.html)
- Guidance for the Risk Based Classification System of In Vitro Diagnostic Devices [2016-09-23] (https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/guidance-documents/guidance-document-guidance-risk-based-classification-system-vitro.html)

- Guidance on Medical Device Compliance and Enforcement (GUI-0073) [2015-06-12] (https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/medical-devices/guidance-medical-device-compliance-enforcement-0073.html)
- Investigator's Agreement in Accordance with Subsection 81(k) of the Medical Devices Regulations [2003-01-10] (Investigator's Agreement in Accordance with Subsection 81(k) of the Medical Devices Regulations [2003-01-10])
- Keyword Index to Assist Manufacturers in Verifying the Class of Medical Devices [2006-09-14] (https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/guidance-documents/guidance-industry-keyword-index-assist-manufacturers-class-medical-devices.html)
- The List of Recognized Standards [2016-10-26] (https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/standards/list-recognized-standards-medical-devices.html)
- Management of Applications for Medical Device Licences and Investigational Testing Authorizations [2001-04-06] (https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/policies/management-applications-medical-device-licences-investigational-authorizations.html)
- Mandatory Problem Reporting Forms For Industry [October 2011] (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting/mandatory-medical-device-problem-reporting-form-industry-adverse-reaction-reporting.html)
- Medical Devices Regulations [http://laws-lois.justice.gc.ca/eng/regulations/sor-98-282/FullText.html]
- Notice - ICH Guidance: E11 Addendum [2018-04-05] (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/efficacy/notice-e11-r1-addendum.html)
- Notice - Applications for Investigational Testing Authorization (ITA), for Medical Devices, in the "Non-eCTD Electronics-Only" Format [2017-01-03] (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/notice-applications-investigational-testing-authorization-medical-devices-non-ectd-electronics-only-format.html)
- Notice - ICH Guidance E6: Good Clinical Practice: Consolidated guideline [1997-09-19] (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/efficacy/good-clinical-practice-consolidated-guideline-topic.html)
- Notice - ICH Guidance E9: Statistical Principles of Clinical Trials [2003-02-10] (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/efficacy/statistical-principles-clinical-trials-topic.html)

- Notice - Release of information about Medical Device Investigational Testing Applications authorized by Health Canada [2013-11-15] (https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/policies/notice-release-information-about-medical-device-investigational-applications-authorized.html)
- Notice: Updated Guidance on the Recognition and Use of Standards under the Medical Devices Regulations [2006-09-22] (http://www.hc-sc.gc.ca/dhp-mps/md-im/activit/announce-annonce/md_notice_standards_im_avis_normes-eng.php)
- Preparation of an Application for Investigational Testing - In Vitro Diagnostic Devices (IVDD) V.3 [1999-02-22] (https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/guidance-documents/cover-letter-application-investigational-vitro-diagnostics-devices.html)
- Recall Policy (POL-0016) [2015-03-05] (https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/information-health-product/drugs/recall-policy-0016.html)
- TCPS 2 (2014) - the latest edition of Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/)

Appendix 3 – Determining when an ITA application is required


Based on the intended use in the labelling, does it fit within the definition of a medical device (see section 2.1.2)?
No
ITA Application is not required
Don't know
Refer to Guidance on the Risk-based Classification System for Non-In Vitro Diagnostic Devices and the Guidance for Industry- Keyword Index to Assist Manufacturers in Verifying the Class of Medical Devices.
If still unsure, contact Health Canada.
Yes
Is the investigation sponsored by the manufacturer?
No
Off-label use; no ITA required (see section 2.3.2)
Yes
ITA Application is required
No
Is the study using a Canadian licensed medical device?
Yes
Is the medical device being used within the scope of its licensed indications for use?
Yes
Is the IT being performed to generate data to support a licence application?
No
ITA Application is not required (see section 2.3.2)
Yes
Consult the Investigational Testing Division
No
Is the development, manufacture, and testing of the device being conducted within a single corporate entity?
Yes
Is testing occurring at more than one site?
No
ITA Application is not required (See section 2.3.2)
Yes
No
ITA Application is required

Appendix 4 - Format for an ITA application

The following is the "non-eCTD electronic-only" format for ITA applications referenced in the Notice - Applications for Investigational Testing Authorization (ITA), for Medical Devices, in the "Non-eCTD Electronics-Only" Format. Some of the sections are not applicable to Class II applications. Empty folders must be deleted before filing to Health Canada. Any other supporting documentation that does not fall into one of the pre-defined folders can be provided in an appendix, but should be clearly referenced in the Executive Summary.

01- Cover Letter & Executive Summary

02- Table of Contents

03- Application Form

04- Pre-submission Correspondence

05- **Introduction**
05.01 Manufacturer or Importer Identification
05.02 Device Identification
05.03 Device Description
05.04 Design Philosophy
05.05 Indications For Use, Intended Use, Contraindications
05.06 Device Labelling
05.07Market History

06- Risk Assessment and Risk Reduction Measures
06.01 Risk Assessment
06.02 Previous Studies
06.03 Alternate Treatments or Testing Options
06.04 Precautions

07- Institutional Information
07.01 Investigator Information
07.02 Curriculum Vitae
07.03 Investigator Agreements
07.04 Name and Address of Institutions
07.05 Research Ethics Board Approval

08- **Study Documents**
08.01 Protocol
08.02 Investigator's Brochure
08.03 Informed Consent Form

09- Appendices

Appendix 5 - Frequently asked questions

Investigational Testing Authorization (ITA) Applications

1. **How do I submit my ITA applications?**

Applications will only be accepted in "Non-eCTD Electronic-Only" electronic format, and may be sent by e-mail to: hc.devicelicensing-homologationinstruments.sc@canada.ca. Please be aware that the maximum email size accepted by the corporate email server is twenty (20) MB, and anything larger should be sent by mail (refer to Appendix 1) on a CD or DVD. If the application package is sent on a CD/DVD, ensure that PDF files are no larger than one hundred and fifty (150) MB to ensure they can be accessed efficiently. For more details, including the required organization of information and file details, refer to the Guidance Document: Preparation of Regulatory Activities in the "Non-eCTD Electronic-Only" Format (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/common-technical-document/updated-guidance-document-preparation-regulatory-activities-non-ectd-electronic-only-format.html#a33).

2. **Can an investigator apply for an ITA?**

Applications must be submitted by the device manufacturer or the importer. However, they may delegate an investigator to serve as the regulatory contact. In the case where the importer or investigator is submitting the application, the manufacturer must sign off the application form (see section 2.3.3 of the ITA guidance document for more details).

3. **Is an ITA required if a doctor intends to use an unlicensed device that s/he invented in a study to treat his own patients?**

Medical devices manufactured and used in a clinical investigation within the same corporate entity are exempt from the requirements of the Medical Devices Regulations. This applies only to cases when the investigation is occurring at a single institution. In the case where the physician is the legal manufacturer of the device, as defined under the Regulations, and the device is being used on-site where the physician practices, and s/he is the only person responsible for conducting the investigational testing, there is no sale occurring as defined under the Food and Drugs Act. The requirements of the Regulations do not apply for these situations and an ITA is not required (see section 2.3.2 of the ITA guidance document for more details).

4. **How do I request changes to my ITA?**

Changes to the device and/or protocol that maintain the original study objectives and would not be expected to alter the risk-profile or negatively impact the integrity of the data collected can be submitted as a request for a revised ITA. Evidence to support the requirements under section 81 and 86 of the Regulations should be provided for all requirements that are impacted by the proposed changes. Requests should be submitted electronically in accordance with the current policy for the submission of ITA applications to: hc.devicelicensing-homologationinstruments.sc@canada.ca, or by mail to Health Canada's postal address (see Appendix 1 and section 2.5 of the ITA guidance document for more details).

5. Is an ITA required for a Class I device?

For a class I device, there is no requirement to apply for an authorization to conduct investigational testing, but the manufacturer must keep a record of the information required by section 81 of the Medical Devices Regulations on file and the study should be conducted in accordance with good clinical guidance (e.g., ISO 14155, GCPs, etc.).

6. Do I need REB approval before I will receive an ITA?

For Class II medical devices, although REB approval must be obtained before study initiation, applicants are not required to provide evidence of written approval from the REB to Health Canada.

For Class III and IV medical devices, applicants are required to provide evidence of written approval from the REB along with study documents referenced in the REB approval to Health Canada prior to study initiation. This approval letter must reference the most current study documents (e.g. protocol and informed consent forms). REB approval should ideally be submitted with the ITA application. However, Health Canada will issue a "Letter of Authorization" for investigational testing, if the application meets the requirements stated in Part 3 of the Regulations and REB approval is not available at the time the ITA application review has been completed.

Prior to study initiation, written REB approval which references the most current study documents must be submitted along with a completed "Application for Revised Investigational Testing Authorization" to hc.devicelicensing-homologationinstruments.sc@canada.ca.

If REB approval references updated study documents, you must submit the following prior to study initiation:

1. a completed form titled "Application for Revised Investigational Testing Authorization"; and
2. updated red-lined and clean copies of the protocol and ICF document versions referenced in the REB approval. Please note that red-lined versions must show all changes made from the Health Canada approved version. If the protocol or ICF versions referenced in the REB do not differ from those indicated in the Letter of Authorization, the REB may be submitted to Health Canada without completing an application form. The information on the REB approval will be verified, and an acknowledgement of receipt will be sent.

7. How long after the study has been completed do I have to keep the documents?

Section 55 of the Regulations requires the manufacturer, importer and distributor to retain the distribution records maintained in respect of a medical device for the longer of:

a. the projected useful life of the device; and
b. two years after the date the device is shipped.

The Regulations do not cover the document retention period for clinical institutions. This period should be in line with institutional policies and provincial regulating bodies for the practice of medicine.

8. Do I need to report an incident that occurred during the investigation?

The qualified investigator is required to report serious adverse events that fall within the scope of Section 59 of the Regulations to Health Canada and to the manufacturer or importer within seventy-two (72) hours of discovery. The manufacturer and the importer of a medical device are required to report to Health Canada incidents that fall under the scope of section 59 of the Regulations within ten (10) days, if the incident has led to the death or a serious deterioration in the state of health of a patient, user or other person, or within thirty (30) days the incident has not led to the death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur. Further details of the reporting requirements are set out under sections 59 to 62 of the Regulations and found in section 2.4.5 of the ITA guidance document.

9. If I previously received an ITA for a re-usable device, can I continue to use it after the investigation is over or use it for a new investigation?

The ITA issued pertains specifically to the device, protocol and number of patients referenced on the authorization. After the investigation has been completed the device should be returned to the manufacturer or importer, decommissioned or disposed of appropriately. If the qualified investigator intends to use the devices under a different study protocol, a new ITA application must be submitted by the manufacturer or importer.

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1 The most current versions of ISO standards take precedence over this guidance document, unless the terms are defined in the Food and Drugs Act and Medical Devices Regulations.

2 Clinical Investigation, Investigational Testing, Clinical Trial and Clinical Study are synonyms.

3 For medical devices, applications must be submitted by the medical device manufacturer.

4 Dorland's Medical Dictionary.

5 Ethics Committee and Institutional Review Board are synonyms.

6 Investigation site and investigation centre are synonyms.

7 The terms "investigational medical device" and "investigational device" are used interchangeably.

8 Although not defined in the Medical Devices Regulations, an individual member of the investigation site team is commonly called "sub-investigator" or "co-investigator".

9 The term "sell," as defined in section 2 of the Food and Drugs Act, is not restricted to commercial or monetary sale and includes transactions without consideration, such as devices provided by the manufacturer to the investigator free of charge.

10 Planned hospitalization for a pre-existing condition, or a procedure required by the Clinical Investigation Plan, without serious deterioration in health, is not considered a serious adverse event.

11 Reference can be made to Guidance for the Interpretation of Significant Change of a Medical Device for general principles in determining significant changes.

12 Health Canada will not accept a scanned copy of the records.

13 While this is not defined in the Medical Devices Regulations for device, the Food and Drug Regulations define a period of 25 years for the retention of records related to drug clinical studies.